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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/580,380	05/26/2000	Bradford W. Gibson	UCSFP001/1584.002	1111

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EXAMINER	
CLOW, LORI A	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/580,380	GIBSON ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,8-14,21-24 and 75-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 8-14, 21-24, and 75-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 9 June 2005, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1, 5, 8-14, 21-24, and 75-82 are currently pending. Claims 2-4, 6, 7, 15-20, and 25-74 have been cancelled.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5, 8-14, 21-24, and 75-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 8 recite "a method of determining the tertiary structure of a protein" in the preamble. However, there is no final step of determining the tertiary structure of a protein. Rather, the claims recite a final step of selecting conformations based on rankings. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 8-14, 21-23, and 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lacroix et al. (Biochemistry (1997) Vol. 36, pages 6270-6282), in view of Mitra et al. (Journal of the American Chemical Society (1979) Vol. 101, pages 3097-3110), in further view of Havel et al. (Biopolymers (1979) Vol. 18, pages 73-81). *This is a new grounds of rejection.*

Lacroix et al. discloses a method for three-dimensional modeling based on chemical cross-linking and homology modeling (page 6272, column 1, Computer-Assisted Three-

Dimensional Homology Modeling) wherein the EDC cross-linked protein is isolated and fragmented by proteolysis (Abstract). The fragmented peptides are identified by mass spectrometry (page 6272, Mass Spectrometry Analysis). The peptides are constrained as to the distance between Gly280 - Met351 from the N-terminus (Figure 5) and the sequences are determined by Edman degradation (Figure 7), as in instant claims 1, 5, and 8.

Scoring values are assigned to fragments having specific distance (Table 1), as in instant claims 5 and 21.

Crossed linked fragments are enriched by fractionation of the reaction mixtures (Figure 1) as in instant claim 14.

The virtual library of proteolyzed products is represented by Table 1, which consists of average mass data (Table 1 and page 6274, column 1, lines 18-24), as in instant claim 22.

The hypothetical structures of the peptides with the predicted protein folds are illustrated in Figures 9-1 1. Further, Lacroix et al. discloses the homology modeling is similar to that of Rossi et al. 1995 (page 6272, column 1, Computer-Assisted Three-dimensional Homology Modeling). Rossi et al. discloses threading" wherein a set of homologous three-dimensional structures is used as a reference template, sequence of proteins are aligned and the candidate structure is identified by comparing the said structure to the reference set (Rossi et al., page 7313, Computer-Assisted Three-dimensional Homology Modeling j, columns 1-2), as in instant claim 23.

Lacroix et al. do not teach the cross-linkers as recited in claims 9-13 or imposing distance constraints on candidate conformations. However, Mitra et al. disclose general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents

(page 3097, Introduction, lines 1-4) such as bifunctional reagents (page 3106, column 2, Discussion, lines 12-13) which react with amines (page 3100, column 1, lines 64-65) as in instant claims 9 and 10.

Two reagents are synthesized wherein one reacts with a nuclease between lysine residues 7 and 37 and the other at 31 and 41 (Abstract etc.), as in instant claims 11 and 12.

The first cross-link is introduced to allow a new conformation for the second link to take place (page 3108, column 1, lines 9-12), as in instant claim 13. It is noted that the first cross-link reaction is optimized to introduce one cross-linker per molecule before the second cross-linker can be introduced.

Mitra et al. discloses reagents such as cross-linking reagents have wide application to the studies of protein structure and the said agents are important tools for biochemist and molecular biologists for protein structure determination (page 31 10, column 1, lines 22-30). Therefore, Mitra et al. suggests that cross-linking reagents are applicable and important tools to determining the tertiary structure of proteins, such as the Clr serine protease of Lacroix et al. Further, Mitra et al teach the need for regulation of the number of cross-linkers per molecule, thus making obvious claims 78-82 (page 3097, Introduction).

Havel et al. teach detecting spatial proximity of distant residues to reduce the range of possible conformations (page 73, Introduction). Doing so enables the "best case" effectiveness of the various kinds of information in deducing the conformation of proteins (page 74, paragraph 1).

One of ordinary skill in the art at the time of the instant invention would have been motivated to use the concept of Mitra et al., for general chemical techniques, to

establish the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction, lines 1-4) and to use the method Lacroix et al. for determining the tertiary structure of a protein with the cross-linking reagents of Mitra et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method for three-dimensional modeling based on chemical cross-linking and homology modeling as taught by Lacroix et al. and use the said method with the cross-linker reagents as taught Mitra et al. Mitra states that his technique has "wide applications in the area of protein subunits, multienzyme complexes, and protein structure" (page 3110, last paragraph) thus motivating one to combine this method with the method of protein structure determination of Lacroix.

It would further have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the crosslinking methods of Lacroix with the chemical techniques of Mitra in the method of Havel. One would have been motivated to do so per the statement of Havel at page 73, which states "a third major avenue detects the spatial proximity of sequentially distant residues (by disulfide bridge determination, crosslinking studies, and nmr)". Further, this enables the "best case" effectiveness of the various kinds of information in deducing the conformation of proteins (page 74, paragraph 1).

Conclusion

Rejections under 35 USC 112, 2nd paragraph, as applied to the previous Office Action, have been withdrawn in view of Applicant's amendments to the claims.

Rejections under 35 USC 112, 1st paragraph have been withdrawn in view of Applicant's response and amendments to the claims.

Rejections under 35 USC 102(b) have been withdrawn in view of Applicant's amendments to the claims.

A new rejection under 35 USC 103 has been set forth.

Claim 24 is free of the prior art because the prior art does not teach or fairly suggest the equation of claim 24.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

August 11, 2005
Lori A. Clow, Ph.D.
Art Unit 1631
Lori A. Clow

MARJORIE A. MORAN
PRIMARY EXAMINER
Marjorie A. Moran
8/11/05